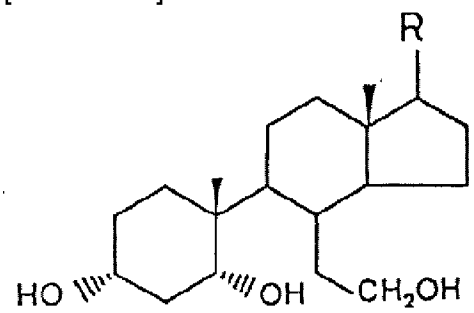
CLAIM + DETAILED DESCRIPTION

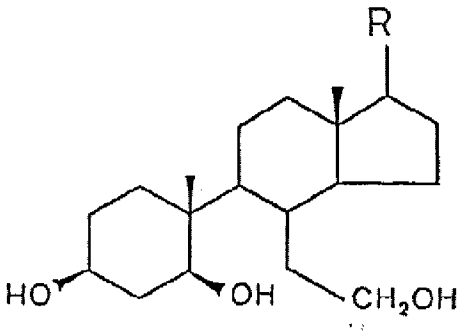
[Claim(s)]

[Claim 1] 5 of 3 alpha-OH expressed with the following formula (1) and (2), 5 alpha-OH or 3 beta-OH, and 5 beta-OH, 6-SEKOSUTE roll derivative.

[Formula 1]



(1)



(2)

(R shows a hydrocarbon group)

[Claim 2] The serum lipid fall agent characterized by containing the sterol derivative of Claim 1, or its salt which can be permitted in pharmacology.

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to a SEKOSUTE roll derivative. Furthermore, it is related with 5 which has characteristic solid structure with this invention useful as a serum lipid fall agent etc., and detailed 6-SEKOSUTE roll derivative.

[0002]

[Description of the Prior Art] Conventionally, various serum lipid fall agents have been developed and put in practical use as a curative medicine of the hyperlipemia which induces arteriosclerosis. However, the conventional serum lipid fall agent did not have an enough improvement operation of lipid metabolism, and was what cannot disregard the side effects, either. For example, it is although clofibrate is known as a serum lipid fall agent currently generally used widely, This clofibrate was not what neutral fat cannot be reduced although serum cholesterol can be reduced to some extent, there is a fault, like those side effects also pose a problem, and can be satisfied practical as a serum lipid fall agent after all. In the use, it was actually obliged to take for a long period of time, being cautious of change of serum lipid.

[0003] For this reason, realization of the new medicine which can improve these faults was desired strongly. In such a situation, these people developed 5 [useful as a new serum lipid fall agent], and 6-SEKOSUTE roll derivative previously, and proposed this (Japanese Patent Application No. No. 118912 [63 to], JP,H1-290624,A). This compound was what the fall activity of neutral fat is good and should attract attention with the fall activity of serum cholesterol.

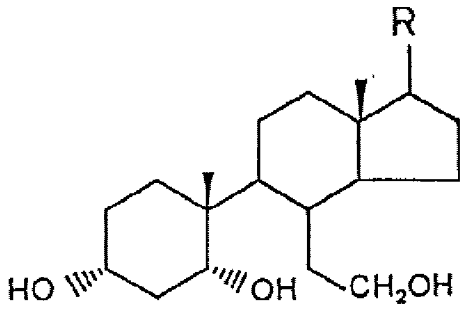
[0004] The place which has advanced examination further about this 5 [new] and 6-SEKOSUTE roll derivative, with what is already proposed, the new substance which moreover attracts attention also about medicinal action, such as that serum lipid fall activity, as another different **** was compounded, and that solid structure became the situation which may actually be used. Then, in order that this invention may cancel the fault of the conventional serum lipid fall agent as above and may develop further the technology about 5 and 6-SEKOSUTE roll derivative, it is made, and it aims at offering the new activity compound which has specific solid structure.

[0005]

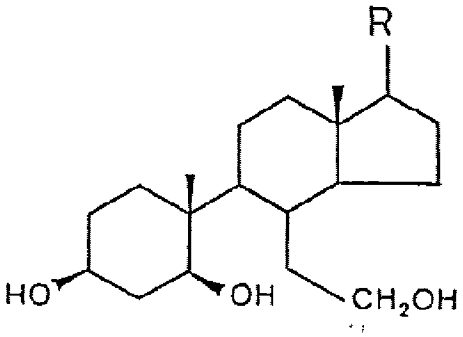
[Means for Solving the Problem] This invention offers 5 of 3 alpha-OH expressed with the following formula (1) and (2), 5 alpha-OH or 3 beta-OH, and 5 beta-OH, and 6-SEKOSUTE roll derivative as what solves the above-mentioned technical problem.

[0006]

[Formula 2]

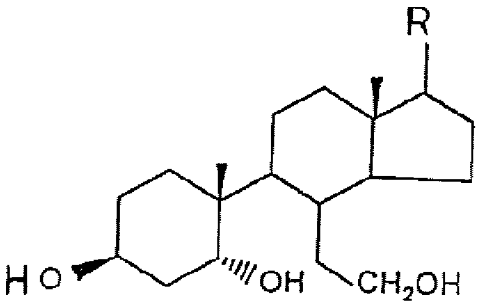


(1)



(2)

[0007] (R shows a hydrocarbon group)
this compound is based on the knowledge that each 5 and 6-SEKOSUTE roll compound indicated by the aforementioned precedence patent application (JP,H1-29064,A) is 3 beta and 5 alpha-OH objects -- these -- that solid structure -- completely -- another different ** -- ****** -- it is proposed. In addition, although R in a formula (1) and (2) is a hydrocarbon group, it can be made into an about [C3 -C10] alkyl group, or an alkenyl group, for example.
[0008] The compound of this invention needs to be unable to manufacture and to adopt the new manufacture method by the method which said precedence patent application is indicating. namely, [derivative / 5 of 3 alpha-OH of the aforementioned formula (1), and 5 beta-OH, and / 6-SEKOSUTE roll] the ozone oxidizing method of cholesterol shown in precedence patent application -- a ******** type -- OH basis of the 6th place of the compound of following (3) 3 beta-OH and 5 alpha-OH can be protected, and it can convert into the ester object which the C-3rd place subsequently reversed, and can manufacture by hydrolyzing and ******(ing).
[0009]
[Formula 3]



(3)

[0010] moreover, [derivative / 5 of 3 beta-OH and 5 beta-OH, and / 6-SEKOSUTE roll] For example, cholest Knoll 6-ON is acetylated and it is Baeyer-Villiger. 5-hydroxy 5 of two kinds of position isomerism lactone objects oxidized and acquired, and 6-****- 5alpha-Colet Stan 6-OIKKU Lactone is isolated. It can manufacture by ****(ing) this in reduction.

[0011] The compound of this invention will not be realized without these methods. For example, 5 expressed with the formula (1) of this invention that can be manufactured as mentioned above, and (2), and 6-SEKOSUTE roll compound are excellent in the both sides of a fall operation of serum cholesterol, and a fall operation of neutral fat. Moreover, since the operation to a liver damage is also lower than the conventional serum lipid fall agent, it is useful as a serum lipid fall agent. In that case, you may use the salt which can be permitted pharmacologically [5 and 6-****- sterol derivative] as a serum lipid fall agent.

[0012] This serum lipid fall agent can be prepared so that it may be suitable for both internal use and parenteral medication. the case where it is used by internal use -- the sterol compound of this invention -- a law -- it forms in powder, granulation, a tablet, a capsule, etc. using a carrier, a diluent base, a dilution agent, etc. by a method. Moreover, when using it by parenteral medication, PH adjustment agent, a preservative, stabilizer, etc. can be added and formed if needed.

[0013] This invention is hereafter explained still more concretely based on a work example.

[0014]

[Example]

Work example 1 (a) Ethanol 10ml was added to the 20g chloroform 500ml solution of 5, 6-SEKOKORE Stan 3beta and 5alpha, and 6-triol cholesterol, and ozone gas was blown at internal temperature-35 degree C for 4 hours. Ozone gas with superfluous blowing in during 10 minutes of argon gas was driven out after checking disappearance of materials by thin layer chromatography. Subsequently, further, it added, and methanol 100ml was added at this temperature, and NaBH4 5g was continuously agitated at room temperature overnight. Acetone 30ml is added after a reaction and it is superfluous NaBH4. It is silica gel column chromatography (chloroform: methanol =20:1) about the residual substance which decomposes, condenses under decompression and is obtained. After refining, it re-crystallized from methanol and 14.9g (68.2% of ****) of notation compounds (TY-04) of the following

physical-properties value were obtained as a colorless needle shape crystal.
[0015] This compound is indicated by said patent application.
[0016]
[Equation 1]
IR ν_{max} (KB $_r$) cm^{-1}: 3300, 2950, 1470, 1380, 1050, 1010.
^{1}H-NMR(CDCℓ_3) δ: 0.65(3H, s, 18-H_3), 0.83(3H, s, 19-H_3), 0.90,
0.94(9H, each s, 21, 26, 27-H_3), 3.77(3H, m, 3α-H, 6-H_2), 4.18
(1H, brs, 5 β- H).

[0017] (b) Chlorination-under ice-cooling trityl 9.8 g was added in the 14.1g PIRIJIN 75ml solution of 5, 6-SEKOKORE Stan 6-Tori Fannie **********- 3 beta, and the 5alpha-JIORU aforementioned compound (TY-04), and it agitated at room temperature after 1-hour churning with this temperature in it overnight. Subsequently, chlorination trityl 1.0 g was added and it agitated at room temperature further for 5 hours. Solvent distilling off was carried out under decompression of a reaction liquid, it dissolved in chloroform and the obtained residual substance was washed in order of dilute hydrochloric acid and a saturation salt solution. It dried with anhydrous magnesium sulfate and solvent distilling off was carried out under decompression. anhydrous [which carries out separation refining of the obtained residual substance by silica gel column chromatography (n-hexane: ethyl acetate =4:1-3:1), and has the following physical-properties value] -- 21.1g (95.6% of ****) of corresponding protection objects were acquired as amorphous.
[0018]
[Equation 2]
IR ν_{max} (KB $_r$) cm^{-1}: 3400, 2950, 1450, 1370, 1050, 700.
H-NMR(CDC ℓ_3) δ: 0.60(3H, s, 18-H_3), 0.83(3H, s, 19-H_3),
0.89(9H, s, 21, 26, 27-H_3), 3.25(2H, m, 6-H_2)3.69(1H, brs, 5β-H),
3.90(1H, m, 3α-H), 7.40(15H, m, trityℓ-H).

[0019] (c) It is the tetrahydro franc 10ml solution of 0.34ml of Gyi acid to the tetrahydro franc 40ml solution of 3alpha-formyloxy 5, 5.0 g of the 6-SEKOKORE Stan 6-truffe enyl ********- 5alpha-all aforementioned protection object, and bird phenyl HOSUFIN 2.4 g. In addition, subsequently the tetrahydro franc 10ml solution of 1.42ml of diethyl azodicarboxylate was dropped, and it agitated for 30 minutes at room temperature. 3.8 g (72.9% of ****) silica gel column chromatography (n-hexane: ethyl acetate =4:1) refines the residual substance condensed and obtained under decompression of reaction liquid -- colorlessness -- the compound of the following physical-properties value was obtained as amorphous.
[0020]
[Equation 3]

IR ν_{max} (KB $_r$) cm^{-1}:3600, 3400, 2950, 1720, 1450, 1160, 1060,
1020, 700. ^{1}H-NMR($CDCl_3$) δ :0.57(3H, s, 18-H_3), 0.83, 0.89
(12H, each s, 19, 21, 26, 27-H_3), 3.28(2H, m, 6-H_2), 3.72
(1H, brs, 5 β-H), 5.15(1H, m, 3α-H), 7.35(15H, m, trityl-H),
8.04(1H, s, HCOO).

[0021] (d) They are diethylether 15ml of generation compound 3.8 g of the account process of ice-cooling Shitamae (c), and 95% ethanol 15ml solution to the 95% ethanol 20ml solution of 5, 6-SEKOKORE Stan 6-Tori Fannie **********- 3 alpha, and 500mg of 5alpha-JIORU sodium hydroxide. It dropped and agitated for 10 minutes at room temperature. Water was added to reaction liquid and it extracted by diethylether. It dried with anhydrous magnesium sulfate after washing with the saturation salt solution, and solvent distilling off was carried out under decompression. 3.7 g colorlessness -- crude C3-EPIMA of the following physical-properties value was obtained as amorphous.

[0022]

[Equation 4]

IR ν_{max} (KB $_r$) cm^{-1}:3400, 2950, 1440, 1060, 1020, 700.
^{1}H-NMR($CDCl_3$) δ :0.59(3H, s, 18-H_3), 0.84, 0.90
(12H, each s, 19, 21, 26, 27-H_3), 3.22(2H, m, 6-H_2), 3.82
(2H, brs, 3 β-H, 5β-H), 7.37(15H, m, trityl-H),

[0023] (e) 5, 6-SEKOKORE Stan 3alpha and 5alpha, and crude C3 of 6-triol above 200mg of bottom of ice-cooling p-toluenesulfonic acid 1 hydration things were added to methanol 20ml of EPIMA 1.7 g, and chloroform 10ml solution, and it agitated for 30 minutes at room temperature. Chloroform was added after the reaction, it washed in order of a saturation salt solution, rare sodium bicarbonate solution, and a saturation salt solution, and solvent distilling off was carried out under decompression after dryness with anhydrous magnesium sulfate. It is silica gel column chromatography (chloroform: methanol =20:1-10:1) about the obtained residual substance. It refined, and re-crystallized with methanol further, and 710mg (it is 42.5% at 2step from **** and a 3alpha-formyloxy compound) of compounds (1) of this invention of the following physical-properties value were obtained as a colorless needle shape crystal.

[0024]

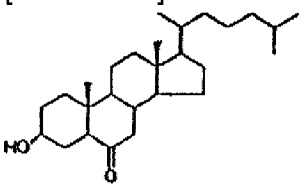
[Equation 5]

IR ν_{max} (KB $_r$) cm^{-1}:3450, 2950, 1460, 1380, 1020,
^{1}H-NMR($CDCl_3$) δ :0.65(3H, s, 18-H_3), 0.83(3H, s, 19-H_3),
0.90(9H, s, 21, 26, 27-H_3), 3.73(2H, m, 6-H_2), 4.01, 4.09
(2H, each brs, 3 β-H, 5β-H)

[0025] Work-example 2(a)3beta-aceto KISHIKORE Stan 6-ON next type (4)

[0026]

[Formula 4]



(4)

[0027] 15ml of bottom acetic anhydrides of ice-cooling were added to the 3.44g PIRIJIN 50ml solution of ** cholest Knoll 6-ON, and it agitated at room temperature for 2 hours. Reaction liquid was condensed under decompression, diethylether was added to the obtained residual substance, and it washed in order of a saturation salt solution, dilute hydrochloric acid, a saturation salt solution, rare sodium bicarbonate solution, and a saturation salt solution. Solvent distilling off was carried out under decompression after dryness with anhydrous magnesium sulfate, and 3.68g of crude compounds of the following physical-properties value were obtained as a colorless crystal.

[0028]

[Equation 6]

IR ν_{max} (KBr)cm^{-1}: 2950, 1730, 1470, 1380, 1240, 1040.

^{1}H-NMR($CDCl_3$) δ : 0.66(3H, s, 18-H_3), 0.77(3H, s, 19-H_3), 0.90, 0.94(9H, each s, 21, 26, 27-H_3), 2.02(3H, s, CH_3OCO), 4.67(1H, m, 3Hα-H).

[0029] (b) The chloroform 40ml solution of 3.92g of m-chloro fault benzoic acid was dropped in the chloroform 90ml solution of 3.67g of crude compounds of the Baeyer-Villiger oxidation reaction aforementioned process (a), and it agitated at room temperature for 24 hours. Subsequently, the chloroform 40ml solution of 3.92g of m-chloro fault benzoic acid was added, and it agitated at room temperature for further 41 hours. Reaction liquid was condensed under decompression, diethylether was added to the obtained residual substance, it washed in order of sodium carbonate, water, and a saturation salt solution 10%, and bottom solvent distilling off of decompression was carried out after dryness with anhydrous magnesium sulfate. It is silica gel column chromatography (n-hexane: ethyl acetate =5:1-3:1) about the obtained residual substance. Separation refining was carried out and 1.10g (it is 20.7% at 2step from **** and cholest Knoll 6-ON) and 813mg (it is 28.0% at 2step from **** and cholest Knoll 6-ON) of compounds (b) were obtained for the compound (a) of Table 1 as a colorless crystal.

[0030]

[Table 1]

3β-Acetoxy-5-hydroxy-5,6-seco- 5α-cholestane-6-oic lactone( )

IR ν_{max} (KBr)cm^{-1}:2950, 1730, 1460, 1360, 1240, 1030.

^{1}H-NMR($CDCl_3$) δ:0.69(3H, s, 18-H_3), 0.83(3H, s, 19-H_3), 0.90,

0.93(9H, each s, 21, 26, 27-H_3), 2.05(3H, s, CH_3OCO), 2.39(2H, m, 7-H_2),

4.26(1H, m, 5α-H), 4.64(1H, m, 3α-H)

3β-Acetoxy-7-hydroxy-6,7-seco- 5α-cholestane-6-oic lactone( )

IR ν_{max} (KBr)cm^{-1}:2950, 1730, 1700, 1460, 1360, 1250, 1200, 1040.

^{1}H-NMR($CDCl_3$) δ:0.69(3H, s, 18-H_3), 0.83(3H, s, 19-H_3), 0.90,

0.93(9H, each s, 21, 26, 27-H_3), 2.03(3H, s, CH_3OCO), 2.90(1H, m, 5α-H),

4.08(2H, m, 7-H_2), 4.59(1H, m, 3α-H)

[0031] (c) Account (compound a) of ice-cooling Shitamae 760mg anhydrous diethylether 50ml solution was dropped to the anhydrous diethylether 50ml soil suspension of 5, 6-SEKOKORE Stan 3beta and 5beta, and 6-triol LiAlH4 700mg, and it agitated at room temperature for 14 hours. The bottom ethyl acetate of ice-cooling is added to reaction liquid, and it is superfluous LiAlH4. It decomposed, and subsequently, dilute sulfuric acid was added and it agitated for several minutes. Water was added to this, the organic layer was isolated preparatively, and the water layer was further extracted by diethylether. The organic layer was washed collectively and solvent distilling off was carried out under decompression after dryness with anhydrous magnesium sulfate. carrying out separation refining of the residual substance obtained by silica gel column chromatography (chloroform: methanol =15:1) -- colorlessness -- 500mg (71.7% of ****) of compounds (2) of this invention that has the following physical-properties value as amorphous were obtained.

[0032]

[Equation 7]

IR ν_{max} (KBr)cm^{-1}:3350, 2950, 1460, 1380, 1050.

^{1}H-NMR($CDCl_3$) δ:0.65(3H, s, 18-H_3), 0.83(3H, s, 19-H_3),

0.90, 1.09(9H, each s, 21, 26, 27-H_3),

3.76(4H, m, 3Hα-H, 5α-H, 6-H_2).

[0033] About the compound obtained according to the three or more-work example work examples 1-2, the lipid fall operation in a high cholesterol foods (HCD) load rat was evaluated. (1) It ****(ed) and prepared in 0.5 % methyl cellulose solution so that the medication capacity of the above-mentioned compound might become about a compound in kg, and 30mg / 5ml / (b. w.).

[0034] In addition, 5ml (b. w.)/kg of 0.5 % methyl cellulose solution was administered orally to the contrast group and the HCD contrast group.

(2) The Wistar system male rat of 5 weeks old of use animals (Japanese Clare) It accommodated five animals at a time in the cage made of TPX resin after purchase (1989. 4.11), and a cubed diet (CE-2, Japanese Clare) and tap water were made to take in freely, and preliminary breeding was carried out for six days at the room temperature of 22**1 degree C, 55**10% of humidity, and the breeding room of 20:00 of Lighting Sub-Division time 8:00-.
[0035] The animal was stratified with weight after the end of preliminary breeding, and one groups [five] divided into each 13 groups so that the average weight of each group might become uniform. Group composition was made into a total of five groups of a contrast group, a HCD contrast group, a TY-04 medication group, and a compound (1) (2) medication group. In addition, he weighed 131-145kg at the time of a group division of a use animal.
(3) While making all the medication groups except a contrast group take in the solid high cholesterol feed (Japanese Clare) which added 1.0 % cholesterol, 0.5 % cholic acid, and 12.0% coconut oil in test method CE-2 feed (usually cubed diet) free for ten days A 30mg/kg sample compound or 0.5 %methylcellulose From 18-hour before of the last medication which carried out continuation internal use of the solution for 1 ten days once per day, an animal is made into a fasting state, 4 hours after the last medication, under anesthesia, it collected blood from the inferior vena cava, and bloodletting fatality was carried out. Then, a liver, the thymus, both spermaries, and both the adrenal glands were extracted, and wet weight was measured. The extracted venous blood is ** which conducted blood biochemistry inspection immediately. Characteristics to be inspected are serum total cholesterol (totalcholesterol;TC), Consider it as five items of neutral fat (triglyceride;TG), HDL-cholesterol (HDL-C), and serum GOT-GPT, and [- (VLDL+LDL) cholesterol count] HDL-C was deducted and calculated from TC and the arteriosclerosis index (athro-genic index;AL) was computed from the TC-HDL-C/HDL-C ratio.
[0036] In addition, weight and the amount of baiting were measured every day in exam time.
(4) In distributions, such as a deed, it is Student at P< 0.05 about statistical processing F official approval. t official approval is used and, in non-******, it is Cochran-Cox. The test of significance was performed using official approval.
(5) As shown in the test result table 2, it is related with TC and HCD contrast groups are 96.8 mg/dl and about 1.4 to 65.6 mg/dl of a contrast group. The twice as many upward tendency as this was shown. The TY-04 medication group showed 14% of increase control tendency in TC, and showed 17% of increase control tendency by the compound (1) medication group of this invention.
[0037] The compound (1) of this invention is useful for applying to a lipid fall. (VLDL+LDL) About -C, the HCD contrast group showed the significant increase in 73.2 mg/dl to 28.2 mg/dl of a contrast group. The TY-04 medication group showed 20% of increase control tendency, and the compound (1) medication group of this invention showed 26% of increase control tendency.

[0038] It is related with A.I. Artificial Intelligence and is 0.757 of a contrast group. It receives and is 3.138 at a HCD contrast group. The significant increase was shown. TY-04 and the compound (1) medication group of this invention showed ****% and 36% of increase control tendency, respectively. About TG, the HCD contrast group showed this value to 30.4 mg/dl of a contrast group. Although TG was controlled 9% by the TY-04 medication group, the compound (2) of this invention showed 18% of significant fall.
[0039] About GOT and GPT, it was the compound (1) of TY-04 and this invention, and compared with the HCD medication group, the significant fall of 16 or 22% of GOT was shown, respectively, and GPT did not show a significant operation in which medication group. In addition, although a significant reduction of GOT was accepted, all are change in a physiological normal variation, and it seems that it cannot involve to a medicine nature liver damage.
[0040]
[Table 2]

評価	Total-cho (mg/dl)	HDL-cho (mg/dl)	VLDL+LDL-cho (mg/dl)	Atherogenic index	Triglycerides (mg/dl)	GOT (IU/ℓ)	GPT (IU/ℓ)
コントロール	65.6±1.5 (68)	37.4±1.2 (158)	28.2±0.9 (39)	0.757 ±0.037 (24)	30.4±3.1 (100)	155.0 ±14.2 (101)	29.6±1.4 (106)
HCD-コントロール	96.8 ±11.4 (100)	23.6±1.1 (100)	73.2±11.5 (100)	3.138 ±0.524 (100)	30.4±1.5 (100)	152.8 ±4.8 (100)	28.0±1.4 (100)
TY-04	83.0 ±4.1 (86)	24.6±1.6 (104)	58.4±2.9 (80)	2.397 ±0.135 (76)	27.6±3.2 (91)	128.2 ±2.4 (100)	30.0±1.0 (107)
	80.8 ±5.6 (83)	26.8±1.1 (114)	54.0±5.0 (74)	2.015 ±0.162 (64)	35.6±5.0 (117)	104.4 ±1.6 (68)	28.0±2.2 (100)
	93.0 ±9.8 (96)	23.4±1.0 (99)	69.6±10.4 (95)	3.040 ±0.511 (97)	24.8±1.7 (82)	131.8 ±13.7. (86)	25.8±1.2 (92)

[Translation done.]

PATENT ABSTRACTS OF JAPAN

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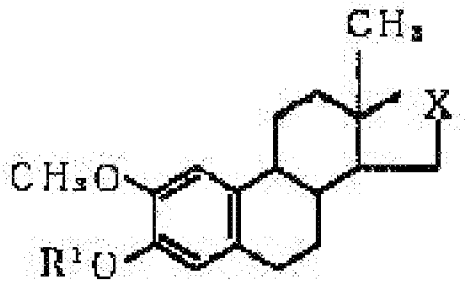
(72)Inventor : **YAGI KUNIO**

(54) ANTI-ARTROTERIOSCLEROTIC AGENT

(57)Abstract:
PURPOSE: TO provide an anti-arteriosclerotic agent capable of suppressing the hyperplasia of the arterial smooth muscle cells, containing, as active ingredient, an estrogen derivative.
CONSTITUTION: This anti-arteriosclerotic agent contains, as active ingredient, a



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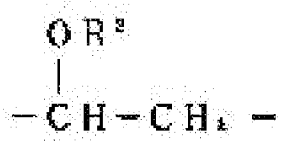

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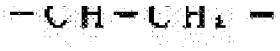

compound of formula I (X is of formula II, etc., R1 and R2 are each H or an acyl such as acetyl or propionyl) which is a metabolite of estrogen as female hormone or a prodrug capable of easily forming 2-methoxyestrogen in vivo and subject to deacylatior in vivo. The compound of formula I is low-toxic, presents no hormonal action, being capable of lowering serum lipoperoxide levels leading to migration of the smooth muscle cells in the intermediate membrane of arterial wall into the inner membrane and preventing the cells from proliferation to cause angiopathy. This agent can be made into a preparation such as a oral agent, injection or percutaneous agent, and its dose is pref. 0.5-10mg/kg b.w./day once or twice a day.